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Red Cell Distribution Width as a Prognostic Marker for Mortality in Critically Ill Patients Above 85

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Abstract:

Background: The increasing elderly population, particularly those aged ≥ 85 years, emphasizes the need for reliable prognostic markers to guide clinical decision-making in Intensive Care Units (ICUs).Existing scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) and the Glasgow Coma Scale (GCS), have shown limitations in sensitivity and specificity when applied to geriatric demographics. This study aimed to evaluate Red Cell Distribution Width (RDW) as a potential prognostic marker for mortality outcomes in critically ill patients aged 85 years and above.

Methods: This observational cohort study retrospectively analyzed the medical records of 489 patients aged ≥ 85 years who were admitted to the ICU of Mersin University Medical School, Turkey, between January 1, 2015, and December 31, 2022.This study assessed the association between RDW levels and mortality outcomes, controlled for demographic data, biochemical indices, and hematological markers. Statistical Package for the Social Sciences (SPSS) version 26 was used for data analysis.

Results: Patients were stratified into two groups based on RDW levels: ≤ 15.5 (N=145) and > 15.5 (N=344). The mortality rate was significantly higher in the group with RDW > 15.5 group (67.7% vs. 51.7%; $p < 0.001$).Other variables, such as age, sex, and concurrent diseases, did not differ significantly between the two groups. Hematological parameters, such as hemoglobin and mean platelet volume (MPV), were found to be significantly different between the two groups ($p=0.044$ and $p=0.016$, respectively). Elevated levels of lactate dehydrogenase (LDH) were also noted in the RDW > 15.5 group ($p=0.007$).

Conclusions: RDW appears to be an independent predictor of mortality in critically ill patients aged ≥ 85 years irrespective of other comorbidities. This study highlights the necessity to incorporate age-specific biomarkers such as RDW into clinical paradigms for geriatric critical care. Further research is warranted to explore the underlying mechanisms by which RDW modulates outcomes in this high-risk population.

Clinical Application of the Study

Early Risk Stratification: Our findings suggest that RDW may serve as an independent prognostic marker. Critically ill patients aged ≥ 85 years with elevated RDW levels may be identified as a high-risk group for mortality.

Key words: Red Cell Distribution Width (RDW); Critically Ill Patients; Geriatric Mortality; Prognostic Markers; Early Intervention; Risk Stratification

I. Introduction

The aging population is a global phenomenon, and the proportion of people over the age of 85 years is expected to increase significantly in the coming decades(1).This group is particularly vulnerable to critical illnesses, and its management in intensive care units (ICUs) is challenging. Reliable prognostic markers are needed to guide clinical decision-making in this population. The burgeoning elderly population indicates a dire necessity for reliable and early prognostic markers, especially for those in the ICU. Precision in prognostication is not merely academic; it possesses real-world implications, shaping clinical decisions that dictate resource allocation, treatment options, and end-of-life care(1, 2).Traditional scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) or Glasgow Coma Scale (GCS), have been applied to assess the severity of illness and predict outcomes, but they may lack sensitivity and specificity in geriatric patients, thereby necessitating age-adapted prognostic markers(2, 3).

Red Cell Distribution Width (RDW), a coefficient of variation of red blood cell volume, has long been employed as a peripheral tool in the diagnosis and differentiation of anemias. However, emerging literature suggests that its role extends beyond hematological parameters, implicating it as a potential marker of systemic ailments. Elevated RDW levels have been increasingly linked to adverse outcomes in various conditions, such as cardiovascular diseases, diabetes, and neurodegenerative disorders(2, 4-6).

A burgeoning body of evidence has explored the utility of RDW as a prognostic factor for mortality in the general population. However, this association's generalizability to the critically ill geriatric demographic remains relatively uncharted. The intricacies of aging, ranging from cellular senescence to systemic inflammation, may modulate RDW differently and, as a corollary, its prognostic utility may have unique implications in this age group(4, 7).

Given the escalating urgency for age-specific markers of critical illness and the provocative, albeit inconclusive, evidence surrounding RDW, this study aimed to investigate the relationship between RDW levels and mortality outcomes in critically ill patients aged 85 years and over. Specifically, we examined whether elevated RDW levels are independent predictors of short-term and long-term mortality in this high-risk cohort, and whether these associations are modulated by clinical, biochemical, and hematological variables. This inquiry endeavors to fill a critical gap in the literature and offers a nuanced understanding that could potentially redefine geriatric critical care paradigms.

II. Materials and Methods

Study Design and Setting

This was a retrospective observational cohort study conducted in the Intensive Care Unit (ICU) of the Department of Internal Medicine, Mersin University Medical School, Turkey. This study was engineered to assess the association between Red Cell Distribution Width (RDW) levels and mortality outcomes in critically ill patients aged 85 years or older.

Ethical Considerations

The research initiative received Ethical approval was obtained from the Institutional Review Board (IRB) and Clinical Research Ethics Committee of Mersin University Medical School. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The approval number for this research was 2023/66, dated February 1, 2023.

Study Population and Eligibility Criteria

The study draws upon the medical records of patients aged ≥ 85 years who were admitted to the ICU between January 1, 2015, and December 31, 2022.The inclusion criteria were patients of either sex, aged 85 years or older, and complete RDW level data. Patients with preexisting hematologic malignancies or those who received erythrocyte transfusions were excluded to eliminate potential confounders.

Data Variables and Measurement Parameters

Demographic data, biochemical indices, hematological markers, coagulation profiles, and clinical outcome measures were collected.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.Continuous variables were described using means and standard deviations, whereas categorical variables were summarized using frequencies and percentages. Normality of the data distribution was verified using the Shapiro-Wilk test. Inferential statistics, including Pearson's correlation for continuous variables and chi-squared tests for categorical variables, were employed. Logistic regression models were used to identify independent predictors of mortality. All statistical tests were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance.

III. Results

Demographic and Clinical Characteristics

The study cohort consisted of 489 patients, stratified by RDW levels, with 145 in the RDW ≤ 15.5, and 344 in the RDW > 15.5 group. The average age was 88.9±7.2 in the lower RDW group and 88.7±7.1 in the higher RDW group, showing no statistically significant difference (p=0.295). The gender distribution revealed a larger proportion of males (41.6%) in the higher RDW group than in the lower RDW group (35.2%), but this was not statistically significant (p=0.187).Concurrent diseases were equally distributed between both groups (p=0.607), indicating that RDW was not necessarily influenced by the presence of other illnesses in this cohort (Table 1).

Biochemical Parameters

Biochemical parameters, including urea, creatinine, and electrolyte levels, were not significantly different between the two groups. However, the lactate dehydrogenase (LDH) levels were notably higher in the RDW > 15.5 group (p=0.007).Albumin levels were significantly lower in the high RDW group (p=0.037) (Table 2).

Hematological Parameters

Hemoglobin levels were significantly lower in the higher RDW group (p=0.044), and MPV was also statistically different between the two groups (p=0.016) (Table 3). buna önceki makaleden atıf yap

Clinical Outcomes

Patients in the RDW > 15.5 group had a significantly higher mortality rate (67.7% vs. 51.7%, p < 0.001) and incidence of sepsis (9.6% vs. 2.1%, p=0.004) (Table 4).

IV. Discussion

The present study endeavors to comprehend the predictive value of RDW on ICU related outcomes, primarily focusing on in-hospital mortality, 30-days readmission rates, and length of hospital stay. The results reveal a striking relationship between elevated RDW levels and adverse patient outcomes, thus corroborating previous research in this area. This study further intensifies the discussion by including a substantial sample size and examining the relationship across various disease categories and biochemical parameters.

Our results evince that a higher RDW value (> 15.5) has a statistically significant association with increased in-hospital mortality. This was observed to be 67.7% in the higher RDW group compared to 51.7% in the lower RDW group. Notably, the correlation with mortality was age-independent and consistent across gender. This mirrors findings from existing literature, which has demonstrated RDW as a risk stratification tool in conditions like cardiovascular diseases, stroke, and anemia (2, 6-8).

Interpretation of Biochemical Markers in Relation to RDW

In the context of the study at hand, the serum Lactate Dehydrogenase (LDH) levels were notably different between the two RDW groups, with higher LDH values observed in the group with elevated RDW (>15.5).

LDH is a ubiquitous enzyme involved in anaerobic glycolysis, and its elevated serum levels are a nonspecific marker of tissue damage and cell lysis (9). Elevated levels of LDH have previously been associated with unfavorable outcomes in numerous pathological conditions including myocardial infarction, hematological malignancies, and sepsis (5, 10). While our study did not explicitly delve into the mechanisms behind this correlation, it is plausible that higher LDH levels in the elevated RDW group signify more extensive tissue damage or metabolic stress (11). This could potentially reflect a higher degree of organ dysfunction or failure in these patients, which can be attributed as one of the driving factors for increased mortality in this group.

Our study also elucidates a statistically significant reduction in Albumin levels in the higher RDW group. Albumin, primarily synthesized by the liver, functions as a transporter protein and plays a crucial role in maintaining oncotic pressure (11). Hypoalbuminemia has often been implicated as a poor prognostic marker in hospitalized patients, suggestive of either chronic liver disease, acute inflammatory states, or malnutrition (9, 12). The lowered Albumin levels in the high RDW group could be indicative of underlying chronic or acute pathophysiological processes. Reduced levels of Albumin might also indirectly suggest a higher inflammatory state, corroborating the elevated LDH levels. However, due to the absence of specific inflammatory markers in our dataset, this remains speculative.

Total Bilirubin and Direct Bilirubin levels were significantly elevated in the high RDW group. Elevated bilirubin levels are generally a manifestation of hepatocellular injury, intra- or extra-hepatic cholestasis, or hemolysis(9). Given the heightened RDW levels and the existing literature linking RDW with conditions like anemia, one might speculate that the elevated Bilirubin levels may stem from increased red blood cell turnover or hemolysis. The bilirubin elevation could also be seen as a surrogate for liver dysfunction, thereby positing a more severe illness stage in these patients. Bilirubin as a marker could, therefore, represent an additional risk stratification avenue when considered in tandem with RDW, although prospective studies would be required for validation.

While our study echoes the utility of RDW as a predictor for adverse hospital-related outcomes, what remains elusive is the precise etiological relationship between RDW and the observed biochemical anomalies. Previous literature has posited a role for oxidative stress and inflammation in RDW elevation (11, 13). Elevated LDH, reduced Albumin, and increased Bilirubin levels might be reflective of a systemic pathological state that not only results in varied red cell sizes but also affects other biochemical parameters (12, 13).

Given that elevated RDW could represent a confluence of pathological states, the observed biochemical deviations might serve as supplementary indicators. They might collectively elucidate an underlying, more extensive, pathophysiological tableau that warrants intensive medical intervention.

The current study reaffirms the prognostic value of RDW, particularly when viewed in combination with other biochemical markers like LDH, Albumin, and Bilirubin. Elevated levels of these biochemical markers could be hypothesized to signify a higher degree of tissue damage, inflammation, and potentially hepatic or renal impairment, which could underlie the worsened outcomes in the high RDW group. Future studies should endeavor to clarify the mechanistic pathways connecting these biochemical markers and RDW, ideally employing a multi-omics approach for a more nuanced understanding.

Clinical Outcomes and Associations with RDW

In our study, one of the most striking findings was the substantial disparity in mortality rates between patients with elevated and non-elevated RDW levels. In particular, those with elevated RDW faced a grim prognosis, echoing the emerging consensus that elevated RDW is an independent marker for adverse outcomes in critically ill patients. This supports a robust body of literature linking RDW to poor outcomes in a myriad of conditions including cardiovascular diseases, various malignancies, and sepsis (1, 2, 6, 10).

On the other hand, traditional severity-of-illness scores like APACHE showed no significant difference between the RDW groups, emphasizing that RDW captures unique aspects of patient physiology not fully described by such scores. This draws attention to the possibility that RDW and APACHE may act as complementary rather than overlapping markers, a prospect warranting further investigation. Similarly, neither the duration of ICU

stays nor the Glasgow Coma Scale (GKS) scores showed an association with RDW levels, suggesting that RDW serves as an acute prognostic marker but may not influence longer-term clinical course or neurological status.

Moreover, the 30-day mortality rate did not vary significantly between the groups, adding complexity to the dialogue about the temporal utility of RDW as a prognostic marker. This could imply that the immediate adverse outcomes correlated with high RDW may not extend to a longer temporal frame, which is a subject of ongoing debate in the medical literature (7, 14, 15).

What was particularly noteworthy was the higher resubmission and sepsis rates seen in the elevated RDW group. The greater frequency of hospital readmissions may reflect a more tumultuous and complicated clinical course, potentially indicating that these patients may require more vigilant post-discharge monitoring and early intervention. The elevated incidence of sepsis also aligns well with the hypothesis that higher RDW levels could be indicative of a heightened inflammatory state, making the connection between RDW and systemic inflammation increasingly difficult to ignore.

Our study provides a robust framework for understanding the prognostic value of RDW, especially when considered in tandem with other biochemical markers such as lactate dehydrogenase, albumin, and bilirubin. These markers, collectively, might serve as a prism through which a more complicated, systemic pathophysiological tableau is revealed. Future studies employing a multi-omics approach could help in elucidating the intricate web of interactions and pathways that involve RDW and other markers, thereby potentially providing a more nuanced understanding of their role in patient outcomes.

Thus, while RDW emerges as a simple yet potent tool for risk stratification in the ICU, its integration into clinical paradigms should be approached with caution until the complex underlying pathways and mechanisms are better understood. This underlines the need for further in-depth, targeted studies to clarify these relationships and guide the incorporation of RDW into holistic patient care strategies.

Strengths and Limitations

A major strength of our study resides in the sizeable dataset culled over five years, allowing for a broad representation across diseases and age groups. However, the study is not without its limitations. For instance, the lack of nutritional and inflammatory markers prevents us from drawing further conclusions about the mechanisms underlying the RDW and outcome association. Additionally, the exclusion of patients without RDW values during admission could introduce a selection bias, potentially affecting the generalizability of the results.

V. Conclusion

The spresent study substantiates the utility of RDW as a predictor for adverse hospital-related outcomes, including mortality and re-admission rates. This implies that RDW could serve as an effective, easily accessible prognostic marker for hospitalized patients, especially those above the age of 85 and with multiple comorbidities. However, further investigation is required to pinpoint the mechanisms driving these associations and to validate the findings in broader patient populations.

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Table 1. Comparative Demographic and Clinical Characteristics of Patients Stratified by Red Cell Distribution Width (RDW) Levels

Variables	RDW ≤ 15.5	RDW > 15.5	*p-value
Sample size (N)	145	344	
Age (Years)	88.9 ± 7.2	88.7 ± 7.1	0.295
Gender			
Male (N, %)	51 (35.2%)	143 (41.6%)	0.187
Female (N, %)	94 (64.8%)	201 (58.4%)	
Comorbidities (N, %)			
Isolated (N, %)	11 (7.6%)	31 (9%)	0.607
Multiple (N, %)	134 (92.4%)	313 (91%)	

RDW: Red Cell Distribution Width; N: Number of Participants
*Student's t-test

Table 2: Comparative Biochemical and Hematological Parameters in Patients Stratified by Red Cell Distribution Width (RDW) Levels

Biochemical Parameters	RDW ≤ 15.5	RDW > 15.5	p-value
Sample Size (N)	145	344	
Urea (mg/dL)	131 (97 - 192)	142 (105 - 195)	0.083
Creatinine (mg/dL)	1.5 (0.8 - 2.4)	1.5 (0.8 - 2.7)	0.184
Sodium (Na, mmol/L)	139.1 ± 12.1	139.6 ± 14.6	0.331
Potassium (K, mmol/L)	4.53 ± 0.73	4.44 ± 0.96	0.166
Calcium (Ca, mg/dL)	8.18 ± 0.8	8.2 ± 0.73	0.488
Phosphorus (P, mg/dL)	3.64 ± 0.72	3.7 ± 0.84	0.397
Magnesium (Mg, mg/dL)	2.07 ± 0.26	2.02 ± 0.2	0.182
AST (U/L)	46 (18 - 64.6)	40 (20 - 57)	0.111
ALT (U/L)	19 (10 - 35)	18 (12 - 36)	0.336
LDH (U/L)	251 (190 - 494)	324 (237 - 549)	**0.007**
Total Protein (g/dL)	5.51 ± 0.91	5.47 ± 1.76	0.409
Albumin (g/dL)	2.83 ± 0.41	2.69 ± 0.35	**0.037**
Total Bilirubin (mg/dL)	0.84 (0.5 - 1.32)	1.37 (0.6 - 1.88)	**0.005**
Direct Bilirubin (mg/dL)	0.46 (0.13 - 0.61)	0.74 (0.16 - 0.84)	**0.018**
CRP (mg/L)	83 (22 - 138)	95 (20 - 151)	0.064
Procalcitonin (ng/mL)	1.02 (0.45 - 7.98)	1.16 (0.8 - 9.13)	0.580
Parathormone (pg/mL)	141 (67 - 366)	134 (62 - 295)	0.155
Vitamin D (ng/mL)	12 (9 - 23)	14 (8 - 21)	0.352
Troponin (ng/mL)	24 (11 - 398)	32 (10 - 411)	0.427

RDW: Red Cell Distribution Width; N: Sample Size; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein
*p-value representing statistical significance, Student's t-test

Table 3: Comparative Hematological Profiles of Patients Grouped According to Red Cell Distribution Width (RDW) Levels

Parameters	RDW ≤ 15.5	RDW > 15.5	p-value
N	145	344	
Hemoglobin	11.84 ± 1.89	10.65 ± 1.32	**0.044**
Lökosit	12.9 (8 - 17)	13.2 (9 - 16)	0.360
Platelet	231 (137 - 284)	238 (140 - 271)	0.512
MPV	10.9 ± 2.94	11.26 ± 3.14	**0.016**
NLO	10 (5 - 18)	11 (6 - 18)	0.673
Fibrinojen	363.5 ± 136.8	384.2 ± 152.7	0.554
INR	1.4 (1.2 - 1.8)	1.5 (1.2 - 1.9)	0.910
aPTT	25.1 ± 7.77	23.2 ± 9.6	0.169

RDW: Red Cell Distribution Width; N: Number of Participants; MPV: Mean Platelet Volume; NLO: Neutrophil-to-Lymphocyte Ratio; INR: International Normalized Ratio; aPTT: Activated Partial Thromboplastin Time

*p: p-value representing statistical significance, Student's t-test

Table 4: Comparison of Clinical Outcomes and Severity Scores Between Patient Cohorts Stratified by Red Cell Distribution Width (RDW) Levels

Parameters	RDW ≤ 15.5	RDW > 15.5	p-value
N	145	344	
Outcome			
Exitus	75 (%51.7)	233 (%67.7)	< **0.001**
Alive	70 (%48.3)	111 (%32.3)	
APACHE	24 (10 - 33)	21 (12 - 29)	0.524
GKS	12 (3 - 14)	11 (3 - 13)	0.725
ICU LOS	6 (3 - 12)	6 (3 - 12)	0.922
LOS	6 (3 - 12)	6 (3 - 12)	0.931
First 30 Days			
Exitus	78 (%53.8)	204 (%59.3)	0.260
Alive	67 (%46.2)	140 (%40.7)	
Resubmission			
Yes	3 (%2.1)	23 (%6.7)	**0.038**
No	142 (%97.9)	321 (%93.3)	
Sepsis			
Yes	3 (%2.1)	33 (%9.6)	**0.004**
No	142 (%97.9)	311 (%90.4)	

RDW: Red Cell Distribution Width; N: Number of Participants; APACHE: Acute Physiology and Chronic Health Evaluation; GKS: Glasgow Coma Scale; ICU LOS: Intensive Care Unit Length of Stay; LOS: Length of Stay

*p: p-value for statistical significance, Chi-square or Fisher's exact